## REMARKS

### I. Status of the Claims

Claims 1-4 are pending in this application.

### II. Rejection under 35 U.S.C. § 112, First Paragraph

The Office maintains the rejection of claims 3 and 4 under 35 U.S.C. § 112, first paragraph, as allegedly not enabled. Office Action at page 2. The Office asserts that "the specification, while being enabling for treating insufficient development and regeneration of blood vessel and various diseases cause[d] by ischemia, does not reasonably provide enablement for *preventing* insufficient development and regeneration of blood vessel and various diseases cause[d] by ischemia." *Id.* (emphasis in original); *see also* Office Action dated December 4, 2009, at page 2. In the Reply to Office Action dated June 4, 2010 ("Reply"), Applicants amended claim 3 to remove the term "preventative," thus rendering the rejection regarding *preventing* moot. Reply at page 4.

The Office now asserts that "[i]t was clearly delineated in the previous office action that it is unclear what is the scope of the claims under 'insufficient development and regeneration of blood vessel and various diseases cause[d] by ischemia.'" Office Action at page 2. Applicants respectfully disagree. In the Office Action dated December 4, 2009, the Office's comments regarding "scope" were directed to *organ damage*: "It is unclear what is the scope of claim 4 under 'insufficient development and regeneration of blood vessel and various diseases cause[d] by ischemia' to including various organ damages accompanied by diabetes mellitus." Office Action dated December 4, 2009, at page 2. Applicants amended claim 4 to remove the phrase

"various organ damages accompanied by diabetes mellitus," thus rendering the rejection regarding *organ damage* moot. Reply at pages 4-5.

The Office therefore appears to now assert a *new* basis for rejection, i.e., "it is unclear what is the scope of the claims under 'insufficient development and regeneration of blood vessel and various diseases cause[d] by ischemia.'" Office Action at page 2. Applicants submit that the finality of this Office Action is improper, as the new basis of rejection is neither necessitated by Applicants' amendments nor based on information submitted in an Information Disclosure Statement. *See* M.P.E.P. § 706.07. Applicants respectfully request that the finality of the Office Action dated August 17, 2010, be withdrawn.

Furthermore, the Office's comments are internally inconsistent with respect to this new rejection. The Office first acknowledges that the specification is enabled regarding treatment for "insufficient development and regeneration of blood vessel and various diseases cause[d] by ischemia," and then asserts that the claims are unclear regarding that very subject matter. Office Action at page 2. The Office asserts that a "disorder of ischemia such as myocardial infarct is irreversible cell death result[ing] from ischemia which is not treatable by angiogenesis," providing no factual support for that premise contrary to the instruction of the M.P.E.P. *See* M.P.E.P. § 2164.04 (requiring the Office to provide "specific findings of fact, supported by [] evidence" to draw conclusions regarding a lack of enablement); *see also id.* § 2144.03 (stating that "[i]t is never appropriate to rely solely on common knowledge in the art without evidentiary support in the record as the principal evidence upon which a rejection was based").

Indeed, teachings in the art do not indicate that myocardial infarction leads to "irreversible cell death" as the Office suggests. Office Action at page 2. For example, in

cardiac infarction, not all of the myocardium in the ischemic area suffers irreversible necrosis; some areas may recover reversibly by producing reversible forms of ventricular dysfunction after reperfusion such as percutaneous coronary intervention or thrombolysis. *See* Gowda, R.M. et al., "Reversible Myocardial Dysfunction: Basics and Evaluation," *Int. J. Cardiol.* (2004) vol. 97, pp. 349-353 ("Gowda") (copy attached). Gowda notes that the substantial potential of coronary collaterals limits the extent of myocardial damage due to ischemia, and this effect depends largely on the rate at which the coronary collateral circulation develops. *See, e.g.*, Sasayama, S. et al., "Recent Insights Into Coronary Collateral Circulation," *J. Am. Heart Assoc.* (1992) vol. 85, p. 1197-1204 (copy attached). Further, the myocardial ischemia triggers collateral growth and develops new collateral circulation upon myocardial infarction. *See id.*

The aim of therapeutic angiogenesis for ischemic heart disease is to promote self-protective angiogenesis exogenously and alleviate myocardial ischemia, thereby avoiding heart failure by saving more myocardial cells and preventing myocardial remodeling. *See* Freedman, S. B. et al., "Therapeutic Angiogenesis for Ischemic Cardiovascular Disease," *J. Mol. Cell Cardiol.* (2001) vol. 33, pp. 379-393 (copy attached). Indeed, Angiopoietin-I is a protein that plays an important role in angiogenesis as well as vascular endothelial growth factor (VEGF). Ye et al., for example, report that expressing angiopoietin-1 in an infarcted area of a porcine model three weeks after coronary artery ligation resulted in promotion of angiogenesis, local blood volume increase, and improved ejection fraction. Ye, L. et al., "Angiopoietin-1 for Myocardial Angiogenesis: A Comparison Between Delivery Strategies," *Eur. J. Heart Failure* (2007) vol. 9, pp. 458-465 (copy attached).

In sum, the Office appears to improperly assert a new ground for this rejection based on enablement in a final Office Action. Moreover, as Applicants discuss above, therapeutic angiogenesis is an effective treatment for myocardial infarction. Accordingly, Applicants submit that claims 3 and 4 are fully enabled and request that the Office withdraw this rejection.

**III. Rejection under 35 U.S.C. § 103**

The Office maintains the rejection of claims 1-4 under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent No. 5,656,642 ("Fujioka") in view of Orito et al. (*J. Pharmacol. Exper. Ther.*, 1999) ("Orito"), Da Silva-Azevedo et al. (*Biochem. Biophys. Res. Comm.*, 2002) ("Silva-Azevedo"), and Zhou et al. (*Cell Tissue Res.*, 1998) ("Zhou") supplemented with Sumi et al. (*Biomed. Pharmacother.*, 2007) ("Sumi"). Office Action at page 2. Applicants continue to respectfully disagree and traverse the rejection.

As an initial matter, the Office once again errs by citing Sumi, which has a publication date after the filing date of the present application. As such, Sumi does not represent the state of knowledge in the art at the time of invention. The Office contends that Sumi provides "factual evidence" that the teachings and motivations referred to in the other references are "indeed expected." *Id.* at 3. The question of whether Sumi provides such "evidence" is irrelevant; a later discovered property cannot make that property obvious retroactively back to the time of the invention. *See* M.P.E.P. § 2141.02 ("Obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established," *citing In re Rijckaert*, 9 F.2d 1531, 28 U.S.P.Q.2d 1955 (Fed. Cir. 1993)). Since a person of ordinary skill in the art would not have had access to the information in Sumi at the time this application was filed, Sumi is improperly cited.

With respect to Fujioka, the Office reiterates the argument that "per ponderous of evidence indicate[s] that [an] adrenergic blocker which has vasodilating activity also result[s] in the downstream angiogenesis (Orito, Azevedo or Zhou)." Office Action at page 3; *see also* Office Action dated December 4, 2009, at pages 3-4. In their previous reply, Applicants noted that the Office's rationale is unfounded in that some adrenergic blockers (e.g., terazosin and doxazosin) exhibit vasodilating activity but do not promote angiogenesis. Reply at pages 7-8 (citing Pan et al. (2003) ("Pan") and Keledjian and Kyprianou (2003) ("Keledjian")). The Office appears to dismiss that inconsistency, however, asserting that

> [t]his is not persuasive because *at the time the invention was made* the teaching, suggestion and motivation were provided by the references. The post dated Sumi et al. provided *factual evidence* that such teaching, suggestion and motivation *indeed* is expected. To obviate an established obviou[s]ness based on prior art, factual evidence supporting unexpectancy commensurate with the scope of the claims must be provided.

Office Action at page 3 (emphasis original). The Office thus improperly confines the rejection to the particular references cited in the previous Office Action. Yet, the M.P.E.P. provides that

> [t]he test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art, and all teachings in the prior art must be considered to the extent that they are in analogous arts. Where the teachings of two or more prior art references conflict, the examiner must weigh the power of each reference to suggest solutions to one of ordinary skill in the art, considering the degree to which one reference might accurately discredit another.

M.P.E.P. § 2143.01. Thus, the Office must consider all the teachings in the art, including contradictory teachings and evidence of unpredictability, in its determination regarding obviousness.

The α1 adrenergic blocker prazosin is associated with shear stress-induced angiogenesis. *See* Zhou at 293; Silva-Azevedo at Abstract. On the other hand, studies show that α1-adrenergic blockers terazosin and doxazosin, which have the same quinazoline structure as prazosin, exhibit vasodilating action but *inhibit angiogenesis*. *See, e.g.*, Pan at 724 (copy attached); Keledjian at 1150 (copy attached). In view of this action, researchers have investigated terazosin and doxazosin for potential therapeutic significance in prostate cancer. *Id.* Thus, contrary to the Office's assertion that "it is the innate nature of such compounds to simultaneously hav[e] the [e]ffect of inducing angiogenesis" (Office Action dated December 4, 2009, at page 4), α1-adrenergic blockers having vasodilating action and a quinazoline structure similar to prazosin do not always enhance angiogenic action.

Further, the compound recited in the present claims is reported to have a higher affinity to the α2-adrenergic receptor than the α1-adrenergic receptor and to exert a potent vasodilating effect as an α2-adrenergic antagonist. *See* Orito at Abstract. This compound exhibits higher affinity for α2B-and α2C-adrenergic receptors among α2-adrenergic receptor subtypes, and is a more selective femoral vasolidator compared to conventional vasolidators. *See* Orito, K. et al., "$\alpha_2$-Adrenoceptor Antagonist Properties of OPC-28326, a Novel Selective Peripheral Vasodilator," *Brit. J. Pharmacol.* (2001) vol. 134, pp. 763-770 (copy attached); Sun, B. et al., "OPC-28326, a Selective

Femoral Vasodilator, is an $\alpha_{2C}$ -Adrenoceptor-Selective Antagonist," *J. Pharmacol. Exp. Ther.* (2001), vol. 299, pp. 652-658 (of record; copy not attached).

The compound recited in the present claims is an antagonist to the α2-adrenergic receptor, which is different from the α1-adrenergic receptor in vascular selectivity and distribution. And, as explained above, the art does not support the premise that an α1-adrenergic blocker having vasolidator action always enhances angiogenic action. Once all of the teachings in the prior art are properly considered together in their entireties, it becomes evident that a person of ordinary skill in the art would not have had sufficient guidance to have contemplated, let alone to have achieved, Applicants' claims.

Finally, Applicants bear no burden to provide "factual evidence supporting unexpectancy" as the Office asserts. Office Action at page 3. The burden does not shift to Applicants unless and until the Office establishes a *prima facie* case of obviousness. M.P.E.P. § 2141(IV). The Office has not done so here.

For at least the foregoing reasons, claims 1-4 would not have been obvious in light of the combination of Fujioka, Orito, Da Silva-Azevedo, Zhou, and Sumi. Applicants respectfully request that the Office withdraw this rejection.

**IV. Rejection for Obviousness-Type Double Patenting**

The Office maintains the rejection of claims 1-4 on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-18 of Fujioka in view of Orito, Silva-Azevedo, and Zhou supplemented with Sumi "for reason of record." Office Action at page 3. That is, the Office applies "[t]he same rational[e] for the finding of prima facie obviousness as delineated in [the § 103(a) rejection]." Office Action dated December 4, 2009, at page 4. For the reasons set forth above with regard

to obviousness, Applicants submit that the Office has not established a *prima facie* obviousness to support this rejection of claims 1-4 based on obviousness-type double patenting. Applicants therefore respectfully request that this rejection be withdrawn.

## V. Conclusion

In view of the foregoing remarks, Applicants respectfully request reconsideration of this application and the timely allowance of claims 1-4.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: January 18, 2011

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